Cognition-Enhancing Drugs

MAXWELL J. MEHLMAN

Case Western Reserve University

New drugs that enhance cognition in cognitively healthy individuals present difficult public policy challenges. While their use is not inherently unethical, steps must be taken to ensure that they are safe, that they are widely available to promote equality of opportunity, and that individuals are free to decide whether or not to use them.

New drugs to treat Alzheimer's disease and other cognitive deficits also may improve cognition in healthy individuals. This hope presents both opportunities and challenges. This article explores the ethical, legal, and public policy implications of these interventions. After reviewing the potential benefits and detriments, it considers and rejects ethical objections to their general use and concludes with policy recommendations to promote safety and efficacy, fairness and equality, and voluntariness.

New Discoveries and Future Prospects

The war on Alzheimer's disease and other cognitive ravages of aging is stimulating an intensive effort to develop drugs to improve cognitive functioning. The U.S. Food and Drug Administration already has approved a number of these drugs, including donepezil (Aricept®), rivastigmine tartrate (Exelon®), galantamine HBr (Reminyl®), and memantine (Namenda®). In addition, the new psychostimulant modafinil (Provigil®) improves alertness, a key factor in cognitive performance.

Address correspondence to: Professor Maxwell J. Mehlman, The Law-Medicine Center, Case Western Reserve University School of Law, 11075 East Boulevard, Cleveland, OH 44106 (e-mail: mjm10@case.edu).

The Milbank Quarterly, Vol. 82, No. 3, 2004 (pp. 483–506)

Two aspects of these drugs are noteworthy. The first is that they improve cognition in healthy individuals, not merely in people with Alzheimer's and other diseases. Modafinil is being tested for use by the military and has been shown to improve the simulator performance of helicopter pilots (Caldwell et al. 2000). Preliminary results from federally funded and industry-supported randomized trials on the performance of airline pilots in flight simulators suggest that donepezil improves performance even in highly functioning individuals (Yesavage et al. 2002).

Second, these drugs may not simply maintain wakefulness or improve recall. Some of them may also improve executive function, "the orchestration of basic cognitive processes during goal-oriented problem solving" (Welsh and Pennington 1988, 202).

The use of drugs and other techniques to enhance cognition is not new, of course. Caffeine has been used as a stimulant for at least a thousand years and is often consumed in extremely high dosages. (The popularity of Starbucks, for example, may be due in part to the fact that a 16-ounce serving of its coffee contains 550 milligrams of caffeine, five times the amount in a regular cup of coffee or in a single No Doz® tablet [see Center for Science in the Public Interest 2003].) Nicotine promotes cognitive abilities (Rezvani and Levin 2001). One study at Duke University, for example, found that nicotine patches significantly improved age-associated memory impairment (Romain 2003). Amphetamines were widely employed by the armed forces in World War II and the Korean War (Stoil 1990) and are still being used by the U.S. military today. Indeed, they have been blamed for friendly fire incidents in Afghanistan (Shankar and Duenwald 2003). Students have long used amphetamines as a study aid (Schrage 1985), with methylphenidate (Ritalin®) being the current cognitive enhancement drug of choice on U.S. college campuses (Babcock and Byrne 2000; Farah 2002; Zielbauer 2000).

The new crop of cognitive enhancement drugs may not raise substantially greater ethical, legal, or social concerns than these more familiar interventions. Modafinil does not appear to be significantly more effective at promoting wakefulness than large doses of caffeine (Wesensten et al. 2001). In addition, the currently available Alzheimer's drugs have side effects that may discourage their use for enhancement purposes. (Aricept®, for example, can cause nausea, diarrhea, insomnia, fatigue, vomiting, muscle cramps, and anorexia [see Pfizer 2004].) The Olympics

and other sports organizations already have testing regimes designed to prevent the use of stimulants (World Anti-Doping Agency 2003).

But the new enhancement drugs are only a first step. The federal government alone is spending more than $480 million a year to combat Alzheimer's disease (NIH 2004), which is bound to lead to the development of more effective and safer modalities that produce enhancement effects in healthy individuals. Scientists have only just begun to understand and manipulate the genetics of cognitive performance. Researchers at the University of Pennsylvania, for example, announced in 1999 that they had genetically engineered mice to improve memory and learning (Tang et al. 1999). Accordingly, it is entirely possible that far more powerful and highly selective cognitive enhancement interventions will become available in the near future.

Promises and Pitfalls

These discoveries could yield enormous social benefits in addition to their impact on disease and aging. Students could become better learners. Improved memory and problem-solving skills could make workers safer and more productive. Scientific researchers could achieve breakthroughs more quickly. Policymakers could respond more effectively to crises. Yet the development of more powerful cognitive enhancements poses serious public policy challenges as well.

Health Risks

Future enhancement drugs, like some of their current counterparts, may be accompanied by deleterious side effects, including toxicity and physical or psychological dependence. These risks may be exacerbated by long-term use, which may be necessary to achieve or maintain the desired enhancement effect. Exotic interventions like genetic engineering could produce especially unusual types of damage. The genetically altered "smart mice" at Penn, for example, are reported to be unusually sensitive to pain (Tang, Shimizu, and Tsien 2001; Wei et al. 2001).

Concerns about the safety of cognitive enhancements will be exacerbated by the lack of safety data. The Federal Food, Drug, and Cosmetic Act requires manufacturers to show that drugs are safe for their intended purposes (21 U.S.C. §355[b][1]). Manufacturers may decide to obtain approval from the U.S. Food and Drug Administration (FDA)

for enhancement claims for drugs initially developed to treat cognitive disorders, and if they do so, they will have to submit data showing that the drugs are safe and effective for enhancement use. For example, Allergan originally obtained FDA approval to market Botox® for blepharospasm, strabismus, and cervical dystonia but then submitted data to substantiate a labeling claim for cosmetic use "for the temporary improvement in the appearance of moderate to severe glabellar (frown) lines" (Allergan 2004).

The law permits physicians to prescribe drugs approved for one purpose for any other purpose, even though the manufacturer has submitted no safety or efficacy data to the FDA substantiating the so-called off-label use. Organized medicine has staunchly defended this prerogative as an exercise of professional autonomy within the practice of medicine, a realm that the FDA has long acknowledged lies outside the scope of its authority (Kessler 1989). Many drugs are widely used for off-label, nontherapeutic purposes, including drugs that improve cognition. According to the manufacturer's own data, for example, almost 350,000 prescriptions for the alertness drug modafinil are being written in the United States every year, even though the only condition for which it was approved until recently was narcolepsy, which affects only about 135,000 people (Cephalon 2003). The law restricts the ability of manufacturers to promote drugs for off-label uses, but the recent case in which Warner-Lambert agreed to pay $430 million to settle charges that it promoted Neurontin® for unapproved uses (U.S. Department of Justice 2004) demonstrates that the practice nevertheless takes place.

Physicians might be counted on to refrain from prescribing unsafe or ineffective cognitive enhancements to their patients, and consumers might avoid using risky drugs on their own, but this presupposes that physicians and the public knew the risk/benefit profiles of the products when they were used as enhancements. Some general safety information about the drugs will be available from studies to support approved uses, but special risks could arise if they were used for enhancement purposes. Unless manufacturers were forced to conduct clinical studies on off-label uses or the government financed trials of its own, these risks would not be known until people started using the products as enhancements. The FDA does require manufacturers to notify the agency of adverse events caused by drugs, regardless of the purpose for which the drug was being used, but these events are believed to be significantly underreported (Lazarou, Pomeranz, and Corey 1998). Physicians might be sued for

malpractice if patients were injured by off-label drugs they prescribed, but the burden is on the plaintiff to establish that the physician behaved unreasonably, and this would be difficult to prove in the absence of data from which a jury could conclude that a reasonable physician should have known that the drug was *un*safe or *in*effective. Persons who were injured by drugs used for off-label enhancement use might file product liability suits against the manufacturers, but a recent clarification of the rules of products liability law, which declares drugs unsafe in design only if they are not safe for any group of patients (American Law Institute 1998), may reduce the future likelihood of success.

Another reason that safety data may be lacking is that some cognitive enhancements, like gingko biloba, may be sold as dietary supplements. The Dietary Supplement Health Education Act (21 U.S.C. §321) permits products to be marketed without safety data so long as they do not claim to treat a specific disease, bear a disclaimer on the label that they are not approved by the FDA, and are taken by mouth (21 U.S.C. §321[ff][1]). Unlike drugs, whose sponsors bear the burden of proving that their products are safe and efficacious before they may be marketed, the burden is on the FDA to show that a dietary supplement is unsafe before it can stop the product from being sold. Moreover, the law does not require dietary supplement manufacturers to report adverse events, and there is little voluntary reporting (U.S. General Accounting Office 2001).

Even if safety data are available, the experience with performance-enhancing drugs in sports demonstrates that individuals may employ cognitive enhancements notwithstanding the risks if they expect that the benefits will be great enough. Athletes use anabolic steroids, for example, despite claims that they can cause serious adverse effects such as heart attacks and liver cancer (NIDA 2002). One writer reported that more than half of the 200 world-class athletes he interviewed told him they would take a drug that would enable them to win every competition for five years and then kill them (Amateur Athletic Association Newsletter 2003).

Individuals who are willing to trade health risks in return for cognitive benefits are especially vulnerable to unscrupulous entrepreneurs who misrepresent the effectiveness of their cognitive enhancement products. Even if ineffective substances are not harmful, their purchase transfers wealth, often from those least able to afford it, to hucksters and frauds. The Federal Trade Commission has the authority to punish advertisers who make false or deceptive claims, but its resources are extremely

limited, especially considering the ease with which products can be hawked on the Internet.

Pressures and Inducements to Use Performance-Enhancing Drugs

The experience with performance-enhancing drugs in sports reveals another problem with cognitive enhancements. One reason that athletes take performance-enhancing drugs is pressure from trainers, coaches, teammates, and competitors. When sprinter Ben Johnson was stripped of his 1988 Olympic gold medal, his coach repeatedly stressed that athletes could not succeed in highly competitive environments without using drugs (Starkman 1991). Similarly, individuals may feel that they are unable to refuse to use cognitive enhancements. Business journals already speculate that employers will require employees to take smart pills on the job (Schrage 1999). The military may issue enhancement drugs to soldiers in combat. A naval flight surgeon manual states that although pilots cannot be required to use amphetamines, those who refuse may be denied the opportunity to fly combat missions (U.S. Navy 2000). Schools under pressure to improve standardized test scores might distribute pills to pupils. Parents may give them to their children. Even if the use of cognitive enhancements is not explicitly mandated, people may feel that they must do so in order to succeed or just to stay where they are in competitive endeavors.

Access

Another concern raised by cognitive enhancements is the unfairness that would result if they were not widely available and if only some people could get their hands on them. The supply may be limited because of the FDA's restrictions on the shipment of experimental drugs or the Drug Enforcement Administration's controls on the amount of controlled substances that may be produced. Even if a sufficient supply existed, the FDA would likely require that new Alzheimer's drugs be available only by prescription, and many people, especially those with low incomes, do not have access to a personal physician (Gold and Kuo 2003). Even if individuals do have access to a physician willing to prescribe a drug for enhancement use, the cost may be prohibitive. The retail cost of Aricept, for example, is about $1,500 per year (Senior Market Advisor 2002).

Obviously, a black market would emerge, but even the street price might be too steep for many to afford.

Conceivably, the cost of cognitive enhancements might be borne by health insurance. Physicians might be willing to prescribe therapeutic drugs for cognitively healthy patients and submit claims for treating cognitive impairment. Moreover, it may be hard to distinguish between therapeutic and enhancement use (Buchanan et al. 2000; Parens 1998; Whitehouse at al. 1997). Assuming for the sake of discussion that IQ is a valid measure of cognitive capacity, would a drug that increased IQ be "therapeutic" for everyone whose IQ was below the population mean? For everyone who had less than the maximum measurable IQ? Since cognitive performance appears at least in part to be a function of one's genetic endowment, should suboptimal cognitive ability be considered a genetic defect? Moreover, many people suffer mild cognitive degradation as they age. This has led to a new diagnostic category, "mild cognitively impaired" (MCI), which has been arbitrarily defined as someone whose performance on neuropsychological tests is greater than 1.5 standard deviations from age-associated norms (Petersen et al. 1999). This automatically makes approximately 1,750,000 people in the United States into sufferers of MCI. Moreover, there is evidence that age-associated cognitive deterioration begins around age 30 (Victoroff 2000). If so, then everyone beyond that age might be regarded as cognitively impaired.

Health insurers might be willing to accommodate this diagnostic creep and cover cognition-improving drugs for a large percentage of their insureds. But the cost might be so great that plans might refuse to expand their coverage beyond a narrow set of extreme cases or refuse to cover certain modalities at all, just as some plans do not pay for Viagra® (Klein and Sturm 2002). Although persons suffering from cognitive dysfunction might be deemed to have a disability as defined in the Americans with Disabilities Act, the courts have interpreted the law to allow insurers to decline to cover entire classes of individuals with disabilities (e.g., *Doe v. Mutual of Omaha*, 179 F.3d 557 [7th Cir. 1999]). State legislatures might respond by enacting so-called state mandates—state laws requiring insurers to cover certain services, such as breast reconstruction after mastectomies—but because of preemption by the Employee Retirement Income Security Act (ERISA), these laws do not apply to employers' self-insured health plans, through which most people get private health insurance. In short, many people who have health insurance may not have coverage for expensive cognitive enhancement

drugs. And this does not take into account the 40 million or so Americans who lack health insurance altogether.

Imagine, then, a society in which the only people who could obtain the powerful new cognitive enhancements were those with access to amenable physicians and the resources to bear the cost out-of-pocket. Cognitive enhancements would be available only to the wealthy, or, if their cost were modest enough, to everyone but the poor. Those who were already relatively better off would gain the advantage of cognitive enhancement. The less well-off would fall further and further behind.

Nonetheless, our system tolerates other sources of inequality. Why should we worry about cognitive enhancement when we permit people to profit from advantages like natural talent and good luck—including the good luck of inheriting wealth or gaining social connections through one's family? One answer is that cognitive enhancement could be so powerful a determinant of social success that it would undermine the foundations of our liberal, democratic society (Mehlman 1999, 2000, 2003). But even if we could accommodate the social inequalities that resulted from cognitive enhancements, the question is whether we should.

Is Cognitive Enhancement Ethically Acceptable?

The answer to this question is best approached by returning to the analogy with performance-enhancing drugs in sports. Opponents of drug use in sports object not only to the health risks and the unfairness if only some athletes can obtain them but also to the fundamental incompatibility between drugs and sports. According to this view, sports values only certain inputs: determination, effort, natural talent, and luck. An athlete who wins because she is driven to succeed spends endless hours in training and practice, has an innate athletic ability, and enjoys the good fortune, say, of having wealthy, supportive parents and avoiding injury is entitled to her medal. Her victory is deserved, worthwhile, "authentic." Conversely, a medal won by an athlete who uses drugs is not deserved; her accomplishment is "inauthentic."

A related argument is that drug use is against the rules of sports. Therefore, athletes who use drugs are cheating, just like the baseball player who "corks" his bat or the marathon runner who begins her race by slipping onto the course at the halfway mark. Moreover, it does not matter *why* the rules prohibit drugs. The organizers and participants

may be worried about the safety hazards of drugs, concerned that some athletes may not have access to them, believe that drug-induced achievements are inauthentic, or just not like the idea of people using drugs for nontherapeutic purposes. The point is that the rules of a sport can be, and often are, completely arbitrary. Why does baseball only permit nine players on the field, instead of five or 11? Even rules that are premised on safety turn out to be highly arbitrary, since it is hard to explain why athletes should be allowed to accept the risk of injury that is inherent in a sport but are not permitted to take comparable risks from drugs. Yet it is entirely appropriate, indeed necessary, for a sport to enforce its rules, since a sport must be played within the rules for it to have meaning as a sport.

As a child, you may have tried to play a game in which the individual players made up the rules to suit them as they went along; no doubt you quickly abandoned it in frustration at its pointlessness. Think of the Queen of Hearts' croquet game in *Alice in Wonderland*.

The rules of sports and games can take a similarly arbitrary stance when it comes to cognitive enhancements. It is entirely up to the international Olympic movement to decide to prohibit amphetamines at the same time that it allows motivational counseling, or for the Spanish Chess Federation to forbid the use of high levels of caffeine at the same time that it continues to allow the inhalation of unlimited amounts of aromatic nicotine outside the playing hall (Associated Press 1999; World Chess Federation 2004). Indeed, it might be interesting to see whether a fully enhanced human chess player could beat the most powerful computer.

But what about outside sports and games? Should cognitive enhancements be prohibited in other competitions in which their use might be advantageous, such as school exams and entrance tests or in the workplace? Should the rules arbitrarily forbid people from voluntarily obtaining an advantage from taking relatively safe, widely available enhancement drugs while at the same time allowing them to profit from remedial and test preparation courses or tutors or to send their children to private schools?

One answer might be that cognitive enhancements can be singled out for objection because they are not natural, customary, or traditional. But clearly, the fact that something is naturally occurring does not mean that it is good or desirable. Many scourges of humanity, from floods and famine to Alzheimer's disease and cancer, are naturally occurring phenomena, yet we do not object to measures to combat them like sandbags,

humanitarian food aid, Aricept®, or effective chemotherapy. Similarly, the fact that something does not occur in nature does not make it bad, or we would eschew everything from shoes to the wheel. Moreover, some substances used as cognitive enhancements, such as caffeine, gingko biloba, and nicotine, do occur in nature. The view that cognitive enhancement drugs are bad because they are not customary or traditional also is not persuasive. Caffeine has been used for centuries. Nor is there any obvious reason why something that has been around for a while—like speed reading courses—should be accepted, but a new pill—say, one that replicates the effect of such courses—should be regarded as evil.

A second objection to cognitive enhancement drugs simply might be to the fact that they are "drugs." This argument associates performance-enhancing drugs with illegal "recreational" drug use and drug abuse. But as noted earlier, cognitive enhancement drugs may be perfectly legal (because they are dietary supplements, have FDA approval for an enhancement indication, or are prescribed for off-label use). Obviously there is nothing inherently "abusive" about people wanting to improve their cognitive performance, and except for someone, for example, who takes a cognitive enhancement drug merely to complete the *New York Times* crossword puzzle, cognitive enhancement use would not be recreational (assuming there is something wrong with recreation). Like some types of illegal drugs, these drugs might be objectionable if they were unsafe or habit forming, but this is not true of all drugs, nor is there any reason to believe that it is true of, or inherent in, cognitive enhancement drugs in particular. A concern might be raised if taking cognitive enhancement drugs led to the use of more abhorrent drugs, but this is another empirical claim rather than a necessary characteristic of cognitive enhancements.

A third objection to cognitive enhancement drugs is that accomplishments achieved through their use are unearned and therefore not worthy of reward. Something can be earned in a number of ways, including hard work, self-sacrifice, or kindness to others. If cognitive enhancement drugs avoided the need for these, the argument goes, then the achievements produced with their help would not be merited.

This argument has a number of flaws, however. First, purchasers may have acquired the money to buy cognitive enhancements through hard work and self-sacrifice. Second, the user must decide what tasks to undertake, and so the decision to do something praiseworthy, rather than,

say, to use the drugs to commit crimes or for other forms of ill-gotten gain, confers merit. Third, individuals are likely to have to expend some effort to produce results even if they take enhancement drugs. Athletes who take steroids, for example, must still work very hard to be competitive. Fourth, we reward accomplishments that result from natural talent and luck that are unearned (except in the minds of people who believe that they are rewards from God for good works and clean living).

Apart from sports and games, there seems to be only one other realm in which the use of cognitive enhancements might be objectionable. That is art, in which how it is produced (its artistry) may be as significant as the outcome. Some people value an object because it is handmade, for example, even if it looks and functions the same as one made by a machine. Assuming a computer could write a good book, the fact that it was written by a computer might repel some people. Listeners may criticize a musician who uses propranolol, a beta blocker drug that reduces performance anxiety (Brantigan, Brantigan, and Joseph 1982), even if the drug is used outside of competition.

If cognitive enhancement drugs have a positive effect on artistic ability, as may well be the case, they might be accused of corrupting the aesthetic value of the art that is produced.

But this brings us to a key point: Outside of sports, games, and perhaps the arts, cognitive accomplishments are valued primarily for the social benefits they confer, not for the manner in which they are achieved. If there is an aesthetic dimension to cognitive achievements, any loss of aesthetic value is easily outweighed by the social value of the accomplishment. A gifted composer who dashes off a beautiful symphony in a jiffy, or a child prodigy who produces a charming sonata with little formal training, produces just as treasured a piece as does someone who took years of music lessons or labored over the score for half a lifetime. The inventor of a pollution-free automobile engine reaps the same financial rewards from her patent if her breakthrough occurred by accident than if it followed from painstaking experimentation. Short of misappropriating someone else's work, the value of the results is what counts. Nor is this an objectionable case of the ends justifying the means; no harm is produced by exceptional ability or serendipitous discovery, except perhaps envy, which arguably is generated by any achievement, including one that is earned by hard work.

The question, then, is whether outside of sports, games, and art, the use of cognitive enhancement drugs is analogous to socially unacceptable

stealing or to socially rewarded natural talent or luck. The answer seems clear: You deserve to win a Nobel Prize if you discover the cure for cancer, whether or not you do so with the aid of cognitive enhancement drugs. Outside the realm of certain games, sports, and arts, there is nothing inherently wrong with cognitive enhancements.

This does not mean, however, that powerful, new cognitive enhancement drugs will be readily accepted. They will change a fundamental aspect of American society by adding to the recipe for social success a fourth ingredient, in addition to natural talent, luck, and exercises of the will like effort and self-sacrifice. The new regime will be especially disorienting because of the singular role that the old formula has played in the development of American society. Instead of the older aristocratic recipe for success based largely on lineage, America from the time of its Revolution embraced a reward structure based on "merit." A farmer's son could become president. In Horatio Alger's books, anyone who tried hard enough could become rich. The merit-based reward structure revolutionized American society, enabled the nation to absorb and profit from its waves of immigrants, and became the framework for Western liberal democracy, which Francis Fukuyama called "the final form of human government" (Fukuyama 1989, 4).

There nevertheless are a number of compelling reasons why we should alter the formula for success to accommodate cognitive enhancements. The first is that it would be too difficult to prevent their use. As discussed earlier, under current law, some may be sold as dietary supplements or, if prescription drugs, approved for enhancement uses or prescribed for unapproved enhancement uses. Cognitive enhancements as a class could be subjected to special prohibitions. An amendment to the Federal Food, Drug, and Cosmetic Act that Congress enacted in 1994, for example, makes it a federal felony to distribute human growth hormone "for any use in humans other than the treatment of a disease or other recognized medical condition" (21 U.S.C. §333). Congress also could preclude the sale of cognition-enhancing drugs as dietary supplements. Any changes in the law, however, would have to overcome powerful dietary supplement and physician lobbies. Like anabolic steroids, cognitive enhancement drugs could be classified as controlled substances, and physicians could be prohibited from prescribing them for nonmedical, enhancement purposes. But the Controlled Substances Act permits the government to designate therapeutic drugs as controlled substances only if they have a potential for abuse and could lead to physical or psychological

dependence (21 U.S.C. §812). Even if the repeated use of a drug to achieve or maintain improved cognitive performance might qualify as psychological dependence, it might not lead to physical dependence, and some drugs might be taken to boost cognition only occasionally, rather than repeatedly. Moreover, the government would have difficulty maintaining that enhancing cognition was an abuse, especially given the legality of caffeine and nicotine. In any event, these highly restrictive approaches require physicians and law enforcement officials to be able to distinguish readily between lawful therapeutic and unlawful enhancement uses of the same substances; yet as pointed out earlier, this distinction is extremely elusive. The government might try to designate an arbitrary cutoff, so that only people below a certain performance level could lawfully employ enhancements, but politicians would find it hard to sustain such an arbitrary determination against political pressure and constitutional challenge, particularly if these drugs contributed significantly to cognitive achievement. The only way to avoid having to distinguish between therapeutic and enhancement uses would be to ban enhancing substances altogether—that is, for both enhancement and therapeutic uses. But given the fact that most of these substances will be developed in the first place to treat dread diseases like Alzheimer's, this is politically unthinkable.

In any event, a law that prohibited cognition-improving products would be virtually unenforceable. A black market is certain to arise. The government could attempt to interdict the manufacture, distribution, and possession of these products in the same way that it tries to halt drugs like marijuana and cocaine, but it is likely to enjoy the same dismal record of success. Furthermore, the last thing the rule of law in this country needs is for an enormous portion of the population to be converted into criminals because they try to become more productive at work or to do better in school. Finally, since a main motivation for banning relatively safe cognitive enhancements would be to prevent people from obtaining an unfair or unearned advantage when they competed with nonusers, the law would have to prevent not only the manufacture, distribution, and possession of these products but also their use in competitive situations. In other words, the government would have to operate a drug-testing program like the Olympics, only vastly more widespread and expensive.

Besides the fact that it would be practically impossible to prevent, there is an even more compelling reason why society should permit the

use of cognitive enhancements. If they were truly safe and effective, they would produce significant societal gains. We want our cancer researchers to have access to whatever will help them find a cure, our pilots to react better to sudden emergencies, and our soldiers to be better able to protect themselves and to carry out their missions. A ban on cognitive enhancements would be bad policy because it would deprive society of immeasurable benefits.

The key question, then, is how to maximize the benefits from cognitive enhancements but minimize the harms.

Promoting Safety and Efficacy

As described earlier, loopholes in current law allow cognition-enhancing drugs to be marketed as dietary supplements or to be prescribed for off-label enhancement use without adequate safety and efficacy data. To plug these loopholes, manufacturers could be required to establish the safety and efficacy of their products for these uses before the products were marketed. Essentially this would convert dietary supplements into full-fledged drugs and transform potential off-label uses into actual labeling claims. But since this would trigger intense opposition from the dietary supplement industry and it might be difficult for regulators to predict the off-label uses of drugs before the drugs were introduced into the market, a more likely approach would be to focus on these safety and efficacy concerns after the products began to be sold.

Targeting safety, Congress could authorize the FDA to require dietary supplement manufacturers to report adverse events to the FDA, so that the agency could remove dangerous products, like ephedra, from the market. The FDA also could be given the authority to require drug manufacturers to submit safety data for unapproved uses of their products that generated substantial sales. Except under the Oregon Death with Dignity Act, which requires physicians to inform pharmacists that they are providing drugs for patient suicides (Ore. Rev. Stat. §127.815[3.01]), there is no current method for determining whether a prescription is being written for an approved or unapproved use. To avoid privacy objections, the FDA could conduct confidential physician and consumer surveys and require manufacturers to produce safety profiles for major off-label uses of approved drugs that the surveys identified. These profiles could be based initially on adverse event reports from

physicians and hospital emergency rooms, with the manufacturers providing compensation for the administrative costs of reporting. If these reports identified a potential safety problem, the FDA could be empowered to require manufacturers to conduct clinical trials to demonstrate safety. Monetary penalties for noncompliance could be calculated to strip the manufacturer of the economic gain from the off-label sales of the product. (Removing the product from the market would be an inappropriate sanction, since it would deprive patients of the benefits from approved uses.) Moreover, the courts could interpret product liability law to make manufacturers who failed to conduct safety studies liable for consumer injuries.

Safety information is only half the equation, however. No drug is completely safe. Regulatory determinations about whether or not to permit a drug to be tested or marketed, professional judgments about whether to recommend or prescribe it, and individual decisions about whether or not to use it all entail a balancing of risks and benefits. In addition to information about safety, people therefore need information about efficacy.

Yet full-scale clinical trials are enormously expensive. Congress has authorized the FDA to accept less-than-complete efficacy data, such as data from only phase I and II investigations, in order to accelerate the availability of drugs to treat AIDS and other serious illnesses, and this approach might be extended to dietary supplements and off-label uses of approved drugs on the theory that otherwise they would lack efficacy data altogether. But this would encourage manufacturers to seek FDA approval only for easy-to-establish labeling claims and leave more problematic indications to the less rigorous process for proving the efficacy of off-label uses. A better option might be to require manufacturers to conduct postmarketing efficacy studies of the enhancement uses of only those drugs or dietary supplements that had been shown by adverse event reports to present a high risk of injury. At the same time, the Federal Trade Commission could be given additional resources to investigate and take action against false or unsupported efficacy claims.

Absent some calamity, it is unlikely that concerns about the safety and efficacy of cognitive enhancement products alone would stimulate a significant shift in the law. But the development of these products is part of the growth of "lifestyle medicine" in general. Collectively, concerns about these products may be enough to overcome industry opposition to the need for more safety and efficacy data.

A separate question beyond how to generate the safety and efficacy data necessary to balance risks and benefits is who should do the balancing. In the case of therapeutic interventions, the traditional approach has been to assign this task in the first instance to regulators and health care professionals and to permit consumers to do their own balancing, such as deciding whether to participate in a medical experiment or to employ a particular treatment, only in the case of options that make it past this initial expert review. Such a paternalistic decision-making model may be harder to justify for enhancement interventions, however, since a physician arguably has no greater expertise than a lay person when it comes to ascertaining whether the benefits of enhancing cognitive performance outweigh the risks. Consumers, therefore, may be entitled to considerable autonomy in deciding whether to use a cognition-enhancing drug despite its risks or when its risks or benefits are uncertain or unknown.

Promoting Fairness and Equality

The availability of powerful cognitive enhancements only to those with enough money or connections raises challenging issues of distributive justice. Already privileged individuals could gain significant advantages in a wide variety of competitive social endeavors.

One solution would be for the government or private philanthropies to provide cognitive enhancements to those in need. But who would this be? It would not be persons who were retarded or otherwise regarded as having cognitive deficits, since presumably they would be entitled to cognition-improving products as therapy. Instead, it would be people whose native cognitive abilities, while within the "normal" range, were lower than those of other people.

At first blush, this idea might seem appealing. Cognitive enhancements would compensate for the undeserved disadvantages of lack of talent and bad luck. They would make everyone more equal, creating a society in which there was greater equality of opportunity. By strengthening the role of effort and self-sacrifice as determinants of social reward, they would make the nation more truly a meritocracy.

But the approach is problematic. To begin with, suppose cognitive enhancements gave people a certain boost in their cognitive ability—say, made them 20 percent smarter. Suppose further that cognitive enhancements were given to all those in the lower half of the "normal" range.

These individuals, along with those with below-normal cognitive ability who received the interventions therapeutically, would move up 20 percentage points. But people in the upper half of the population range who obtained enhancements on their own would move up as well. The entire population would move upward in terms of cognitive ability, but the disparities created by natural talent and luck would remain. More realistically, however, due to people's genetic and environmental differences, cognitive enhancement drugs are likely to affect people differently, to be more efficacious in some and more hazardous in others. Some users might see a 40 percent improvement in cognitive ability; others, only a 5 percent improvement. Cognitive enhancements, therefore, could make social success even more a product of undeserved factors than it is now. This could be avoided if enhancements raised everyone's cognitive ability to the same ceiling or if some way were found to handicap those who gained greater cognitive abilities from enhancement than others. But neither of these scenarios is realistic: the former as a matter of biology and the latter because we are unlikely to force people to relinquish the cognitive advantages they obtain from natural talent and luck, even assuming we could design and operate the elaborate, intrusive testing and handicapping system that would be necessary (Vonnegut 1968).

A better approach would be to permit cognitive enhancements to be available on the open market for those who can afford them and to subsidize access to them for those who cannot. This would avoid the economic and social costs of attempting to ban these products, which ultimately would be futile, or of having government or some other party try to identify and distribute enhancements only to persons with a cognitive need. By making these products widely available, society would gain the benefits of the achievements they made possible and reduce or at least refrain from exacerbating the inequalities that stemmed from differences in wealth. Cognitive enhancements would be subsidized only if they were approved by the FDA as safe and efficacious, thereby promoting the development of safer and more effective products and generating safety and efficacy data to inform individual decision making. Both the government and the private sector could subsidize access, the former through Medicare and Medicaid and the latter through private health insurance. Public- and private-group purchasing programs could drive down the costs of the products. If they were safe enough that physicians were not required as decision-making intermediaries, the products ultimately could be sold cheaply over-the-counter.

This approach is not as radical as it may sound. Medicaid and private insurers no doubt already are paying for enhancement uses of drugs like Ritalin®. More important, many private insurers pay for Viagra®, which is widely used for enhancement purposes, and in 1998, the federal government ordered state Medicaid programs to cover the drug (Goldstein 1998). To ensure the widest possible coverage by private third-party payers and avoid ERISA preemptions of state mandates, Congress could make coverage of cognitive enhancements a federal mandate, similar to the requirement that all third-party payers pay for at least a 48-hour hospital maternity stay (Newborns' and Mothers' Health Protection Act 1996). Obviously this would still leave those without public or private health insurance to rely on their own financial resources, but Congress could take the same approach it adopted in 1972 to cover kidney dialysis under the Medicare End Stage Renal Disease Program and make cognitive enhancements available to everyone under Medicare. The government also would have to force down the price of the drugs. If the drugs cost the same as the current retail price of Aricept® and every American took them, the total cost would be approximately $350 billion a year.

Reducing Pressures and Inducements to Use Performance-Enhancing Drugs

The more effective cognitive enhancements prove to be, the more pressure people will feel to use them to gain or retain socioeconomic advantages. So long as resources remain scarce and continue to be apportioned to such a large extent competitively, this type of inducement will persist. As discussed earlier, since the only ways to reduce this pressure—banning cognitive enhancements or discounting the achievements they facilitate—would be highly impractical, the best response would be to ensure that the substances were as safe as possible.

Since no drug is completely safe, however, the question remains whether individuals can be compelled to take cognition-enhancing drugs. The strongest case can be made for persons whose cognitive performance could have a substantial impact on public safety, such as transportation workers or nuclear power plant operators. Instead of requiring these individuals to take drugs, minimum cognitive qualifications could be established for these jobs, which drug use could enable individuals to meet.

In non-safety-critical employment settings, the primary purpose of enhancement drugs would be to increase productivity. To the extent that drug use resembles other techniques to increase productivity, such as employee-training programs, employers might seem entitled to mandate use of the drugs. But drugs are biomedical interventions. A better analogy, therefore, might be employees' wellness programs. Presumably because these programs affect employees' health and bodily integrity, the rules of the Equal Employment Opportunity Commission prohibit employers from requiring employees to participate in them or punishing employees if they refuse (EEOC 2000). Since cognition-enhancing drugs are likely to be accompanied by greater health risks than wellness programs, it would seem even less appropriate for employers to require their use. This does not mean that employers will have to forgo the productivity gains from the use of these drugs, however, but only that they will have to allow employees to use the drugs voluntarily.

What about the military? Military service can subject individuals to extraordinary risks, even death. But there are limits to the extent of these risks. For example, in the absence of special circumstances and a presidential order, soldiers cannot be required to participate in medical experiments (10 U.S.C. §1107[f]). Yet the exigencies of combat probably justify requiring soldiers to use cognition-enhancing drugs unless they are highly dangerous.

Should parents be allowed to give cognitive enhancement drugs to their children? Note that they already are, since no law prohibits parents from feeding their kids caffeinated colas or coffee. If the new enhancement products were deemed safe enough to be sold over-the-counter or added to foods, parents should have the right to give them to their children as well. In fact, the law currently seems to give parents much greater leeway: Clearly, some of them are giving Ritalin® to their children for enhancement purposes, yet Ritalin® is classified as a Schedule II controlled substance, meaning that it has a high potential for abuse and may lead to severe psychological or physical dependence (21 U.S.C. §812[b][2]).

Even if enhancement drugs were extremely safe, control over use by minors should remain with their parents (or, as with caffeine, perhaps with the minors themselves). Although enhancement use might facilitate classroom learning or improve test scores, schools should not be permitted to require children to use them. There is currently a considerable backlash against schools' pressuring parents to give Ritalin® to pupils

perceived to be disruptive (Strawn 2003). In a culture in which children are at risk from illicit drug use, requiring children to use enhancement drugs is likely to be viewed as morally objectionable.

Conclusion

This article has argued that for the most part, competent adults should be free to decide whether or not to use cognition-enhancing drugs, and if these drugs are sufficiently safe and effective, the government should subsidize access to them. It thus is important that the public have valid and reliable safety and efficacy data for these products. The greater the safety hazards are, the greater should be the justification required for anyone, including the government, employers, or parents, to mandate their use.

Some cognitive enhancement products may be so dangerous that society would be justified in outlawing their use in certain cases. Giving them to children, for example, could be deemed child abuse and neglect. However, given the potential societal benefits from cognitive enhancements, the difficulties of interdicting them, the traditional rights of adults to accept risks as long as they do not impose undue costs on third parties, and the liberty of parents to raise their children as they see fit, the government should bear a heavy burden before imposing highly restrictive regulatory prohibitions.

References

Allergan. 2004. Botox® Labeling Indications. Available at http://www.botoxcosmetic.com (accessed February 2, 2004).

Amateur Athletic Association Newsletter. 2003 (December). Available at http://www.aafla.org/10ap/SportsLetter-14-4/SLhome.html (accessed February 2, 2004).

American Law Institute. 1998. *Restatement (Third) of Torts: Products Liability*, §6(c).

Associated Press. 1999. Chess: Drug Testing Has Arrived. *New York Times*, November 16, D7.

Babcock, Q., and T. Byrne. 2000. Student Perceptions of Methylphenidate Abuse at a Public Liberal Arts College. *Journal of American College Health* 49:143–5.

Brantigan, C., T. Brantigan, and N. Joseph. 1982. Effect of Beta Blockade and Beta Stimulation on Stage Fright. *American Journal of Medicine* 72(1):88–94.

Buchanan, A., D.W. Brock, N. Daniels, and D. Wikler. 2000. *From Chance to Choice: Genetics and Justice*. New York: Cambridge University Press.

Caldwell, J.A., Jr., J.L. Caldwell, N.K. Smythe, and K.K. Hall. 2000. A Double-Blind, Placebo-Controlled Investigation of the Efficacy of Modafinil for Sustaining the Alertness and Performance of Aviators: A Helicopter Simulator Study. *Psychopharmacology* 150:272–82.

Center for Science in the Public Interest. 2003. *Health Action Newsletter: The Caffeine Corner: Products Ranked by Content*. Available at http://www.cspinet.org/nah/caffeine/caffeine_corner.htm (accessed November 17, 2003).

Cephalon, Inc. 2003. *Investor Overview*. Available at http://www.corporateir.net/ireye/ir_site.zhtml?ticker=CEPH&script=2100 (accessed November 12, 2003).

Equal Employment Opportunity Commission (EEOC). 2000. EEOC Enforcement Guidance on Disability-Related Inquiries and Medical Examinations of Employees under the Americans with Disabilities Act (ADA) Q.22. Available at http://www.eeoc.gov/policy/docs/guidance-inquiries.html (accessed February 5, 2004).

Farah, M. 2002. Emerging Ethical Issues in Neuroscience. *Nature Neuroscience* 5(11):1123–9.

Fukuyama, F. 1989. The End of History? *National Interest* 16:3–18.

Gold, M., and S. Kuo. 2003. Mathematica Policy Research, Inc.: Access to Physician Services in Public Insurance Programs for Low-Income Populations: A Framework for Assessment and Action. Available at http://www.fdhc.state.fl.us/affordable_health_insurance/PDFs/accessphys.pdf (accessed February 4, 2004).

Goldstein, A. 1998. U.S.: Medicaid Must Cover Viagra. *Washington Post*, July 3, A21.

Kessler, D. 1989. The Regulation of Investigational Drugs. *New England Journal of Medicine* 320:281–8.

Klein, R., and H. Sturm. 2002. Viagra: A Success Story for Rationing? *Health Affairs* 21(6):177–87.

Lazarou, J., B.H. Pomeranz, and P.N. Corey. 1998. Incidence of Adverse Drug Events in Hospitalized Patients: A Meta-Analysis of Prospective Studies. *Journal of the American Medical Association* 279:1200–1205.

Mehlman, M. 1999. How Will We Regulate Genetic Enhancement? *Wake Forest Law Review* 34:671–714.

Mehlman, M. 2000. The Law of Above Averages: Leveling the New Genetic Enhancement Playing Field. *Iowa Law Review* 85:517–93.

Mehlman, M. 2003. *Wondergenes: Genetic Enhancement and the Future of Society.* Bloomington: Indiana University Press.

National Institute on Drug Abuse (NIDA). 2002. Research Report Series: Anabolic Steroid Abuse. Available at http://165.112.78.61/ResearchReports/Steroids/anabolicsteroids3.html (accessed February 2, 2004).

National Institutes of Health (NIH). 2004. NIA and Alzheimer's Association Join Forces Promoting Major AD Genetics Initiative. Available at http://www.alz.org/ResourceCenter/FactSheets/FSNIAGeneticsInitiative.pdf (accessed February 2, 2004).

Newborns' and Mothers' Health Protection Act. 1996. P.L. 104–204.

Parens, R., ed. 1998. *Enhancing Human Traits: Ethical and Social Implications*. Washington, D.C.: Georgetown University Press.

Petersen, R., G. Smith, S. Waring, R. Ivnik, E. Tangalos, and E. Kokmen. 1999. Mild Cognitive Impairment: Clinical Characterization and Outcome. *Archives of Neurology* 56:303–8.

Pfizer. 2004. Aricept® Package Insert. Available at http://www.pfizer.com/download/uspi_aricept.pdf (accessed February 2, 2004).

Rezvani, A.H., and E.D. Levin. 2001. Cognitive Effects of Nicotine. *Biological Psychiatry* 49(3):258–67.

Romain, G. 2003. Nicotine Patches Memory Problems. Available at http://www.betterhumans.com/News/news.aspx?articleID=2003-12-05-4 (accessed February 4, 2004).

Schrage, M. 1985. Soon Drugs May Make Us Smarter, but If We Use These "Brain Steroids," Will Nobel Laureates Need Urine Tests? *Washington Post*, February 3, C1.

Schrage, M. 1999. Performing Poorly? The Solution's a No-Brainer: Just Pop a Smart Pill! *Fortune*, April 26, 426.

Senior Market Advisor. 2002 (March). Will Brand Loyalty Equal Savings? Available at http://www.seniormarketadvisor.com/Archives/mar02/advisory.cfm (accessed February 5, 2004).

Shankar, T., and M. Duenwald. 2003. Bombing Error Puts Spotlight on Pilots' Pills. *New York Times*, January 19, A1.

Starkman, R. 1991. Can Johnson Come Back? *Toronto Star*, January 5, B1.

Stoil, M. 1990. Amphetamine Epidemics: Nothing New. *Addiction and Recovery* 10(1):9.

Strawn, M. 2003. Recent Developments in Direct Consumer Advertising of Attention Disorder Stimulants and Creating Limits to Withstand Constitutional Scrutiny. *Journal of Contemporary Health Law and Policy* 19(2):485–520.

Tang, Y., E. Shimizu, G. Dube, C. Rampon, G. Kerchner, M. Zhuo, G. Liu, and J. Tsien. 1999. Genetic Enhancement of Learning and Memory in Mice. *Nature* 401:63–9.

Tang, Y., E. Shimizu, and J. Tsien. 2001. Do "Smart" Mice Feel More Pain or Are They Just Better Learners? *Nature Neuroscience* 4(5): 453.

U.S. Department of Justice. 2004. Press Release: Warner-Lambert to Pay $430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion. Available at http://www.usdoj.gov/usao/ma/presspage/May2004/Warner-Lambert-globalsettlemnt.htm (accessed May 24, 2004).

U.S. General Accounting Office. 2001. *Health Products for Seniors: "Anti-Aging" Products Pose Potential for Physical and Economic Harm*. Washington, D.C.: U.S. Government Printing Office.

U.S. Navy. 2000. Performance Maintenance during Continuous Flight Operations. Available at http://www.globalsecurity.org/military/library/policy/navy/misc/NAVMEDP-6410.pdf (accessed April 7, 2003).

Victoroff, J. 2000. Evolution and Brain Aging. *Reinsurance Notes* 2(4). Available at http://azlweb01.allianzlife.com/imgate.nsf/0/d5a2ea46935563480625698c006d3062?OpenDocument (accessed February 4, 2004).

Vonnegut, K. 1968. *Harrison Bergeron*. In *Welcome to the Monkey House*, 7–13. New York: Delacorte.

Wei, F., G. Wang, G. Kerchner, S. Kim, H. Xu, Z. Chen, and M. Zhuo. 2001. Genetic Enhancement of Inflammatory Pain by Forebrain NR2B Overexpression. *Nature Neuroscience* 4(2):164–9.

Welsh, M.C., and B.F. Pennington. 1988. Assessing Frontal Lobe Functioning in Children: Views from Developmental Psychology. *Developmental Psychology* 4(3):199–230.

Wesensten, N., G. Belenky, M. Kautz, D. Thorne, R. Reichardt, and T. Balkin. 2001. Maintaining Alertness and Performance during Sleep Deprivation: Modafinil versus Caffeine. *Psychopharmacology* 159:238–47.

Whitehouse, P., E. Juengst, M. Mehlman, and T. Murray. 1997. Enhancing Cognition in the Intellectually Intact. *Hastings Center Report* May/June: 14–22.

World Anti-Doping Agency. 2003. World Anti-Doping Code: 2004 Prohibited List §S1. Available at http://www.wadaama.org/docs/web/standards_harmonization/code/list_standard_2004.pdf (accessed February 2, 2004).

World Chess Federation. 2004. FIDE Tournament Rules §VIII. Smoking Ban. Available at http://www.fide.com/official/handbook.asp?level=C0608 (accessed February 5, 2004).

Yesavage, J.A., M.S. Mumenthaler, J.L. Taylor, L. Friedman, R. O'Hara, J. Sheikh, J. Tinlenberg, and P.J. Whitehouse. 2002. Donepezil and

Flight Simulator Performance: Effects on Retention of Complex Skills. *Neurology* 59:123–5.

Zielbauer, P. 2000. New Campus High: Illicit Prescription Drugs. *New York Times*, March 24, A1.

Acknowledgments: The author would like to thank Eric Juengst, Peter Whitehouse, and Dale Nance for their helpful comments.